Remarks

Claims 1-14, 16, 24-25, 27, 31, 37, 47 and 52 were pending in the subject application. By this Amendment, Applicants have amended claim 52. Accordingly, claims 1-14, 16, 24-25, 27, 31, 37, 47, and 52 are currently pending and under examination.

Restriction

In the October 6, 2006 Office Action, the Examiner acknowledged Applicants election with traverse of Group I, current claims 1-13, 24-25 and 52, as drawn to the elected invention peptide SEQ ID NO. 6. Applicants are pleased to acknowledge that the Examiner rejoined claims 16, 27, 31, 37 and 47. Thus, only claim 14 has been withdrawn from consideration, while claims 1-13, 16, 24-25, 27, 31, 37, 47 and 52 are and under examination.

Claim 14, however, being drawn to a method of use of an elected product, should be rejoined pursuant to 37 C.F.R. §1.141(b) as applicants pointed on page 16, second full paragraph, of their July 27, 2006 Amendment.

Claim Objections

In the October 6, 2006 Office Action, the Examiner objected to the following:

a) claims 1-13, 16, 24-25, 27, 31, 27, 47, and 52 for amendments allegedly not commensurate in scope with the elected invention (namely elected peptide of the invention, comprising SEQ ID NO: 6); and

b) claims 1 and 11 for describing a "composition" within the claims, but "...the pharmaceutical composition has a pH..." within the preamble of the claims.

Applicants' Response:

a) In response, as described in detail herein, applicants respectfully submit that their invention reciting the species of SEQ ID NO. 6 is patentable. Pursuant to M.P.E.P. § 809, *et seq.*, other species shall now be examined.

b) In response, applicants have amended claims 1 and 11 to recite "pharmaceutical composition" instead of "composition".

Double Patenting

On page 8 of the October 6, 2006 Office Action, the Examiner provisionally rejected claims 1-13, 16, 24-25, 27, 31, 37, 47, and 52 under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-18, 21, 31-32, 41, 52-53, and 57-61 of copending Application No. 10/758,572. The Examiner alleged that the conflicting claims are not patently distinct from each other.

In response, applicants defer discussion of this provisional rejection until copending Application No. 10/758,572 issues, or until the obviousness-type double patenting rejection is the only rejection remaining in the present application. M.P.E.P. §804(I)(B)

Rejection Under 35 U.S.C. §112

On page 9 of the October 6, 2006 Official Action, the Examiner alleged that claims 16, 27, 36, 37, 47, and 52 are indefinite for failing to particularly point out and claim the subject matter of the invention. Specifically, the Examiner questioned what amount of time is predetermined; how long the temperature is maintained at -40°C and -45°C, respectively; what the predetermined time is; and what the reduced pressure is that lyophilizes the pharmaceutical composition.

In response, without conceding the correctness of the Examiner's position, applicants have amended claims 16 and 27 to no longer recite "at a predetermined concentration" in step a, and "a predetermined amount of" in step b. Applicants have further amended claim 52 to no longer recite "a predetermined amount of".

In addition, applicants submit that the subject specification provides examples of suitable amounts of time required for practicing the invention, in addition to examples of reduced pressures required to practice lyophilization of the pharmaceutical composition. Furthermore, one of skill in the art would understand, and be able to practice the invention in the absence of descriptions of specific lengths of time, and specific reduced pressures.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 16, 27, 36, 37, 47 and 52 under 35 U.S.C. §112, second paragraph.

Claim Rejections Under 35 U.S.C. 103

On pages 3-7 of the October 6, 2006 Office Action, the Examiner set forth three (3) rejections under 35 U.S.C. §103, each of which is based in the first instance on the combination of U.S. Patent Application Publication No. 2004-0127408A1 (Mozes), and U.S. Patent No. 5,997,856 (Hora). The second of the three rejections further relies on Anderson and Flora (Chapter 34, pages 739-754, *The Practice of Medicinal Chemistry*) to reject claims 10 and 11. The third of the three rejections further relies on U.S. Patent No. 5,134,127 (Stella) to reject claims 6-7 and 13.

Applicants' Reply

In response, Applicants respectfully submit that the claimed invention is an inventive combination which is neither taught nor suggested in the prior art. Furthermore, Applicants respectfully point out that the combination of references is improper, and even if it were proper, fails to teach every element of applicant's invention. Table 1 below briefly summarizes the prior art mentioned by the Examiner and the primary deficiency of each. A full discussion follows.

Table 1

Reference	General Comment
U.S. Pub. No. 2004-0127408A1 (Mozes)	Cyclodextrin not disclosed.
U.S. Patent No. 5,997,856 (Hora)	Solubility problems not disclosed
Anderson and Flora	No discussion of improving peptide solubility at biological pH
U.S. Patent No. 5,134,127 (Stella)	Peptides not mention

Prior Art Does Not Teach Solubility Problem For Recited Peptide

Each of the three obviousness rejections is fundamentally deficient for failing to explain why prior to Applicants' invention one of skill in the art would 1) look for any solubility enhancing agent for the specific recited peptide, and 2) select a substituted β-cyclodextrin as a solubility enhancing agent over any other from the multitude of available solubility-enhancing agents.

Prior to Applicants' invention, a solubility problem for the recited peptides was not disclosed in the prior art; clearly, therefore, the prior art did not provide a solution to the problem. Applicants were first to recognize the solubility problem; applicants were also first to select a substituted β-cyclodextrin as a solubility enhancing agent over the multitude of other available solubility-enhancing agents as a novel solution to the problem. This clearly constituted an inventive step.

MOZES

The Examiner did acknowledge that WO/2002/067848A2 "Mozes" does not explicitly disclose a pharmaceutical composition comprising a pharmaceutically acceptable salt of a peptide and a substituted β-cyclodextrin. Applicants are claiming a new composition in which a peptide is combined with β-cyclodextrin to result in an improved composition having a higher concentration of the peptide.

Mozes clearly, a) does not indicate that there is any solubility problem, and b) teaches that "derivatives and

salts" can "modify...stability, solubility" (page 18, lines 26-28). A cyclodextrin as claimed by Applicants is neither "derivatives" nor "salts". Applicants therefore, maintain that the need for a cyclodextrin, or of any solubility enhancer at all, is simply not taught or alluded to by Mozes.

Thus, there is nothing of record except hindsight motivating the combination of the peptide of Mozes with any solubility enhancer at all (not to mention a β-cyclodextrin). This is a fundamental deficiency of the rejection. The current record fails to identify a suggestion in the prior art to combine the recited peptide with any solubility enhancing agent, much less a cyclodextrin. The current record offers not explanation of why one would look at the cyclodextrin art.

The '856 Patent to Hora et al.

The '856 patent discloses a method and compositions for solubilization of polypeptides, especially proteins. The '856 patent defines "polypeptides" as amino acid polymers containing more than 20 peptide linkages (21 amino acids) and "proteins" as very large polypeptides (column 12, lines 58-61). The '856 patent distinguishes "polypeptides" from "oligopeptides", which have between 2-20 peptide linkages (3-21 amino acids)(column 12, lines 59-61).

The '856 patent focuses on solubilization of "proteins", not on solubilization of "peptides". The '856 patent does not even acknowledge that the solubilization of peptides or of peptide salts is a problem. The '856 patent also does not exemplify solubilization of a peptide, or of a peptide salt.

Finally, the '856 patent does not teach use of sulfobutylether-β-cyclodextrin.

Motivation to combine Mozes and the '856 patent is lacking

There exists no motivation to combine Mozes and the '856 patent. First, as noted above, Mozes discloses "peptides" (within the context of the '856 patent) whereas the '856 patent provides a solubilization method targeting very large polypeptides. As such, the Examiner's stated rationale for combining the two references does not apply.

Second, and more importantly, Mozes does not identify that solubility is a problem with any of its peptides. Mozes mentions salts on page 7, paragraph 0088, as something that can be used to "modify" solubility of the peptide. Applicants' claims recite a salt of a peptide. From the disclosure of Mozes, the solubility of a salt of its peptides appears satisfactory. The peptides are in fact used in the examples of Mozes without any apparent solubility problem.

Thus, absent hindsight, there is no reason of record motivating the combination of the salt of the peptide of Mozes with any solubility enhancer, much less the ones of the '856 patent. This deficiency alone makes the obviousness rejection improper.

Selection of cyclodextrin is unexplained

The Examiner provides no reason whatsoever explaining why one

would select β-cyclodextrin over any other from the multitude of available solubility-enhancing agents. In their own formulation development Applicants tested over forty (40) different solubility enhancers to find several that could improve the solubility of a recited peptide (see pages 23-31 of the subject application) before selecting a β-cyclodextrin.

Therefore, one of skill would not expect that the solubility of the recited peptide would be improved by β-cyclodextrins.

In this regard, Applicants point out that cyclodextrins, and specifically β-cyclodextrins, were known to have less than desirable pharmaceutical properties:

> "The renal toxicity of the parent cyclodextrins is not completely understood. The parent cyclodextrins are reabsorbed and concentrated in the renal tubule where they can interact with and extract cholesterol and other lipid membrane components from cellular structures. A combination of the reabsorption and concentration of both the relatively less soluble parent cyclodextrins and the insoluble cyclodextrin/cholesterol complexes may contribute to the demise of cellular integrity. Precipitates of the cyclodextrin or cyclodextrin/cholesterol complexes have been observed during the course of cellular degeneration, but it is unclear how or if they promote the destruction of the cell. [Hepta-(sulfobutyl ether)-β-cyclodextrin] was designed to improve the safety profile of cyclodextrins." Innovative Drug Delivery Technology for Enhance Solubility and Stability, CAPTISOL Informational

Brochure, CyDex, Inc. (2004)(**Exhibit A**).

Cyclodextrins are not a common class of solubility enhancers, and have known problems, as described above. As such, cyclodextrins would not be the common choice of a solubility enhancer. Therefore, Applicants' selection of a cyclodextrin for enhancing the solubility of a recited peptide is clearly inventive over the prior art. As such, there could not have been a reasonable expectation of success that the peptide of Mozes be formulated with cyclodextrin, and certainly not β-cyclodextrin.

Even if Mozes and the '856 patent are combined, there is no expectation of success

Even in the absence of the required motivation but to explore hindsight, applicants contend that nothing more than an "obvious to try" rationale has been presented in support of the rejection of record. Specifically, assuming the record did contain a motivation to manufacture a pharmaceutical composition (comprising an aqueous carrier, a pharmaceutically acceptable salt of the peptide and β-cyclodextrin derivatives), one skilled in the art would have no expectation that doing so would result in a composition having improved solubility.

An obviousness analysis requires taking into consideration whether or not one of ordinary skill in the art would have an expectation of success. M.P.E.P. §2144.08. "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a

reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (emphasis added).

Applicants have described the difficulty of selecting an appropriate solubility enhancer to improve the solubility of a claimed peptide on page 45, line 27 to page 46, line 6 of the subject application. Applicants summarize testing of a variety of solubility enhancers, most of which were unsuccessful. Only after significant development and testing could an appropriate solubility enhancer be selected to improve the solubility of a claimed peptide. Certainly one could not have expected success with a β-cyclodextrin before such testing. This deficiency alone makes the obviousness rejection improper.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw all three rejections in so far as each is improperly based on Mozes and the '856 patent.

Mozes in view of the '856 patent and Anderson et al.

In response, applicants point out that this rejection suffers from the same deficiencies as the rejection based on Mozes in view of the '856 patent. Anderson et al. fails to remedy any of the deficiencies noted above.

Furthermore, Anderson et al. offer nothing of relevance for formulating a pharmaceutical composition containing the claimed peptide at physiological pH. As summarized on page 45, line 27 to page 46, line 6 of the specification, many

solubility enhancers had to be tested. However, none of the solubility enhancers achieved adequate solubility at physiological pH. Solubility was only reached at pH levels below 3 and above 9 (Specification page 46, lines 1-2). Not until applicants used a β-cyclodextrin was solubility improved at physiological pH.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection based on Mozes, the '856 patent and Anderson et al.

Mozes in view of the '856 patent and the '127 patent

In response, applicants point out that this rejection suffers from the same deficiencies as the rejection based on Mozes in view of the '856 patent. The '127 patent fails to remedy any of the deficiencies noted above.

Furthermore, the '127 patent offers nothing of relevance to the obviousness determination of the claimed invention. The '127 patent discloses use of sulfoalkyl ether cyclodextrin derivatives as solubilizing agents for water insoluble small molecule drugs for parenteral administration, not peptides. The '127 patent does not even mention peptides or proteins, much less exemplify their solubilization. As such, there is no suggestion or motivation to modify or combine the '127 patent with Mozes or the '856 patent

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection based on Mozes, the '856

patent and the '127 patent.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorneys invite the Examiner to telephone at the number provided below.

No fee, other than the enclosed $1,020.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicant
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

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Gary J. Gershik 3/3/07

John P. White Date
Reg. No. 28,678
Gary J. Gershik
Reg. No. 39,992

EXHIBIT A

Applicants: Sharon Cohen-Vered et al.
Application No.: 10/758,397
Filed: January 14, 2004

INNOVATIVE DRUG DELIVERY TECHNOLOGY

FOR ENHANCED SOLUBILITY AND STABILITY

Captisol®
[Sulfobutylether-7-Beta-Cyclodextrin]

Solubility and so much more.

Applicants: Cohen-Vered et al.
Serial No.: 10/758,397
Filed: January 14, 2004
Exhibit A

CAPTISOL-ENABLED® PRODUCTS ARE ON THE MARKET

A PROVEN SOLUTION TO INSOLUBILITY AND INSTABILITY

The successful development of drugs is a complex process from discovery and evaluation through development and commercialization. Captisol provides a useful, simple and proven solution to solubility and stability hurdles faced at each phase of the process.

Combinatorial chemistry, high throughput screening (HTS) and molecular genetics have led to an increase in the number of insoluble and unstable molecules, including peptides and proteins, being investigated for their therapeutic activity.

Using Captisol early in the development process can increase the number of candidates that can be evaluated, decrease development time and increase candidate survivability.

Captisol enables biocompatible formulations for administration parenterally, orally, ophthalmically, via inhalation and other routes. Upon administration, the Captisol-drug complex rapidly disassociates.

Captisol also enhances the oral bioavailability of poorly water soluble drugs if solubility and dissolution are limiting factors.

CAPTISOL - THE TECHNOLOGY

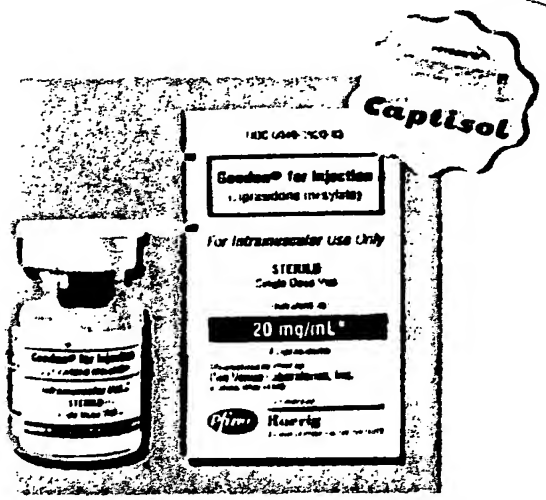
Captisol is a patent protected, uniquely modified cyclodextrin, whose chemical structure was rationally designed to maximize safety and optimize complexation to improve solubility and stability of insoluble drugs.

Captisol Molecular Structure

Captisol is a polyanionic beta-cyclodextrin derivative with a sodium sulfonate salt separated from the lipophilic cavity by a butyl ether spacer group, or sulfobutylether (SBE). The selection of the SBE7-beta-CD as the cyclodextrin with the most desirable safety profile and drug carrier properties was based upon evaluations of the mono, tetra and hepta-dominated substituted preparations (SBE1, SBE4, and SBE7). Captisol is the trade name for CyDex's SBE7-beta-CD preparation.

Captisol has been shown to be safe when administered parenterally, orally and via inhalation and does not exhibit the nephrotoxicity associated with beta-cyclodextrin.

Relative to beta-cyclodextrin, Captisol provides comparable or higher complexation characteristics and superior water solubility in excess of 90 grams/100 ml – a 50-fold improvement.



CAPTISOL IN APPROVED PRODUCTS

Captisol-Enabled® Pfizer products IV Vfend® and IM Geodon® are approved in the US and EU.

	IV Vfend®	IM Geodon®, Zeldox®
Generic	Voriconazole	Ziprasidone
MW	349	563
Indication	Fungal infections	Psychosis
S_0 (Intrinsic Solubility)	200mcg/mL	0.3mcg/mL
Captisol/vial	3200mg	294mg
Captisol/70kg patient	9g/day (maintenance)	588mg/day

Captisol is a multi-platform enabling technology

- *useful for NCEs and line extensions*
- *that enhances solubility, stability and dissolution*
- *for immediate and modified release formulations*

CAPTISOL DESIGNED TO BE SAFE, EASY AND EFFECTIVE

ACCEPTED SAFETY

Captisol's safety studies have successfully supported regulatory filings using Captisol formulations. They are documented in a Type V Drug Master File (DMF) on file with the FDA.

Captisol was designed to maximize safety by eliminating the damaging effects produced by parent cyclodextrins.

The renal toxicity of the parent cyclodextrins is not completely understood. The parent cyclodextrins are reabsorbed and concentrated in the renal tubule where they can interact with and extract cholesterol and other lipid membrane components from cellular structures. A combination of the reabsorption and concentration of both the relatively less soluble parent cyclodextrins and the insoluble cyclodextrin/cholesterol complexes may contribute to the demise of cellular integrity. Precipitates of the cyclodextrin or cyclodextrin/cholesterol complexes have been observed during the course of cellular degeneration, but it is unclear how or if they promote the destruction of the cell.

Captisol was rationally designed to improve safety

Captisol was rationally designed to improve the safety profile of cyclodextrins. The anionic SBE group was introduced to prevent the reabsorption and concentration of Captisol by utilizing the kidney's ability to rapidly excrete ionic compounds. The design of Captisol overcomes the limitation of the low solubility of beta-cyclodextrin and also minimizes the complexation of cholesterol and other lipid cell membrane components resulting in a highly biocompatible drug delivery system.

In-vitro experiments and *in-vivo* acute and subchronic toxicity studies have provided safety data to support the development of Captisol drug formulations in man.

STRAIGHTFORWARD BIODISTRIBUTION AND ELIMINATION

Upon administration, the Captisol-drug complex rapidly disassociates. Captisol formulations are biocompatible and can be administered by numerous routes including parenteral, oral, ophthalmic and inhalation.

Upon I.V. administration Captisol exhibits limited plasma protein binding and distributes to extracellular fluid. I.V. doses of ^{14}C labeled Captisol (rats, mice, dogs, rabbits and humans) were rapidly and completely cleared intact from the circulation. Excretion was primarily in urine, with clearance approximating the glomerular filtration rate.

- While Captisol or Captisol-drug complex is not significantly absorbed after oral administration, drug absorption can be dramatically improved if drug solubility is the limiting factor.
- Captisol is absorbed after inhalation and eliminated via the kidneys.

PHARMACOLOGICALLY INACTIVE

Captisol produced no pharmacological effects on the cardiovascular system; autonomic or somatic functions; respiratory capacity; or fluid or electrolyte excretion upon I.V. administration in a variety of animal models.

EASY

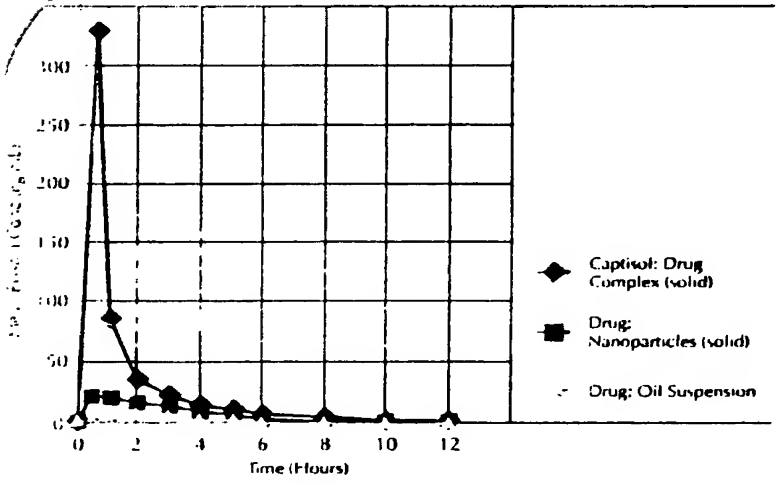
Compared to other drug delivery technologies Captisol is easy to use in your laboratory. Neutral, cationic and anionic drugs have been effectively complexed by Captisol. Aqueous solubilities have increased by a factor of 10 to 25,000, depending on the compound.

In contrast to other solubilization technologies, the feasibility of Captisol can be rapidly assessed with a few simple experiments.

Commercialization is made easy because CyDex's business is to assist in creating viable formulations which utilize the Captisol technology.

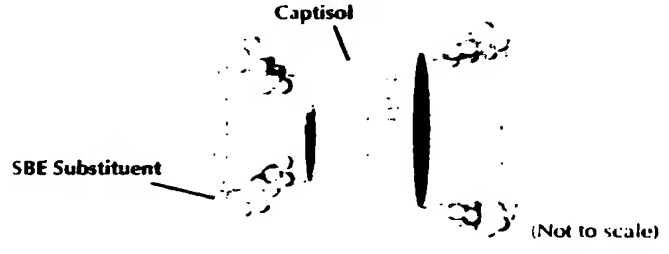
Captisol is easy to use in your laboratory.

Solubility Enhanced Absorption: *A Captisol Solid Formulation vs. Suspension vs. Nanoparticle Formulation*



EFFECTIVE

The SBE group and degree of substitution were selected after years of research to select the best candidate for complexation with a variety of drug molecules. The extended beta-cyclodextrin cavity and anionic nature of Captisol provide additional attributes for successful complexation.



HOW IT WORKS

The SBE substituents on Captisol enhance complexation by providing an extended hydrophobic cavity and an extremely hydrophilic exterior surface.

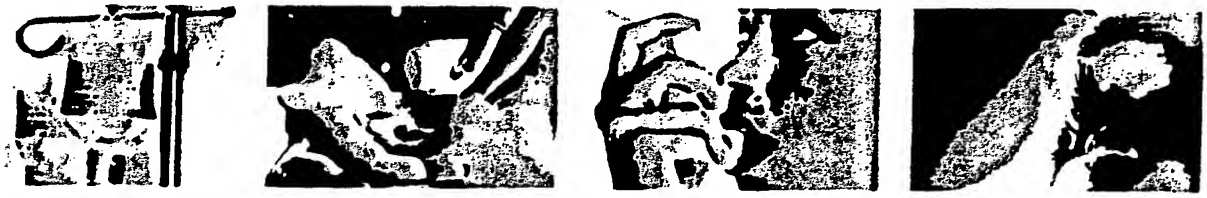
PARENTERAL, ORAL, PULMONARY, OPHTHALMIC APPLICATIONS

DIVERSE DELIVERY METHODS AND THERAPEUTIC APPLICATIONS

PARENTERAL

The two Pfizer products, Vfend®[1] and Geodon®[2], have established the use of Captisol for parenteral formulations.

Solubility enhanced absorption



ORAL

Poorly water-soluble drugs are often dropped from development due to poor oral bioavailability. In oral formulations, Captisol can provide solubility enhanced absorption. This can be especially true for compounds with ionizable groups subject to changes in solubility due to pH changes throughout the gastrointestinal tract.

Captisol can be used in oral solutions as well as oral solids – immediate release and modified controlled release such as osmotic dosage forms. For some compounds, Captisol affords taste-masking. Captisol can be incorporated into a solid dosage form either as a physical mixture or as a complex formed with the drug. A Captisol drug complex can be isolated using lyophilization, spray-drying or by application onto another substrate.

Oral solid Captisol formulations can be made in standard oral processing equipment. Compression characteristics place processed or spray-agglomerated Captisol and Captisol granulations somewhere between Avicel and lactose in compactibility. Flow properties are easily controlled with the type of granulation process and the type of milling used. Tablets made with Captisol can be film coated using standard formulations and processing techniques.

PULMONARY

Captisol is being used to solubilize insoluble drugs for administration via inhalation. Short-term safety studies are complete. Initial research shows dramatic improvement in amount delivered, time of delivery and drug-loading in smaller droplet sizes. The ability to reproducibly generate smaller droplet sizes that contain solubilized drug may result in the delivery to the deep lung areas.

OPHTHALMIC

Insoluble drugs have been formulated into aqueous solutions for ophthalmic administration. Currently, one product has advanced to clinical development.

CLIENT SUPPORT

Obtaining Captisol Material
Small samples of Captisol can be made available free of charge to first time users. Captisol is available for preclinical studies after signing an appropriate confidentiality agreement. Additional research quantities can be purchased directly from CyDex.

Clinical and commercial quantities are available from a validated manufacturing process. Captisol is produced under cGMP conditions.

Formulation Services
CyDex associates are committed to assisting you in rapidly getting *Captisol-Enabled*® products to market. We offer formulation development services on an as needed basis to our clients. CyDex is committed to moving projects forward rapidly to assist clients in capturing important first-to-market status.

Analytical
Captisol is well characterized and supported by validated analytical methods. Specification limits are in place for residual starting materials, average degree of substitution, process impurities, water content, and heavy metals among others. Captisol is provided as a low bioburden material. Data are available that demonstrate Captisol is remarkably stable for years under a variety of conditions.

Licensing
Captisol is a proprietary technology. Initial evaluations of Captisol may be conducted under the terms of a confidentiality agreement. A limited use agreement or commercial license and supply agreement with CyDex must be executed before client companies begin clinical trials. Licenses or options will be negotiated on a compound by compound basis. The basic agreement structure includes a fee upon signing, milestone payments and royalty on product sales.

CyDex
CyDex, Inc. offers advanced drug delivery solutions to bring important new medications to patients by developing its own pipeline of *Captisol-Enabled*® proprietary drug formulations and by partnering with the world's leading pharmaceutical and biotechnology companies. CyDex has agreements with Allergan, Inc.; Bristol-Myers Squibb; Taisho, of Japan; Merck & Co., Inc.; OSI Pharmaceuticals, Inc.; Pfizer, Inc; OncoPept, of Switzerland; Teva Pharmaceutical Industries Ltd., of Israel and TargeGen. CyDex is a privately owned company located in suburban Kansas City. To learn more about our partnerships and pipeline, visit www.cydexinc.com.

CyDex was established in 1993 to license and commercialize modified cyclodextrins for use in drug development and formulation. These cyclodextrins were originally synthesized and patented by scientists from the University of Kansas. CyDex holds the exclusive commercial license to the SBE cyclodextrins and is seeking licenses to other derivative cyclodextrin technology.

CyDex, Inc.
10513 West 84th Terrace
Lenexa, KS 66214-1643
(913) 685-8850
fax: (913) 685-8856
www.cydexinc.com
www.captisol.com